How does male circumcision protect against HIV infection?

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In his otherwise excellent review of the AIDS epidemic in the 21st century, Fauci presented no new strategies for preventing the spread of the disease.[1] He made no mention of male circumcision, yet there is now compelling epidemiological evidence from over 40 studies which shows that male circumcision provides significant protection against HIV infection; circumcised males are two to eight times less likely to become infected with HIV.[2] Furthermore, circumcision also protects against other sexually transmitted infections, such as syphilis and gonorrhoea,[3 4] and since people who have a sexually transmitted infection are two to five times more likely to become infected with HIV,[5] circumcision may be even more protective. The most dramatic evidence of the protective effect of circumcision comes from a new study of couples in Uganda who had discordant HIV status; in this study the woman was HIV positive and her male partner was not.[6] No new infections occurred among any of the 50 circumcised men over 30 months, whereas 40 of 137 uncircumcised men became infected during this time. Both groups had been given free access to HIV testing, intensive instruction about preventing infection, and free condoms (which were continuously available), but 89% of the men never used condoms, and condom use did not seem to influence the rate of transmission of HIV. These findings should focus the spotlight of scientific attention onto the foreskin. Why does its removal reduce a man's susceptibility to HIV infection?

Summary points

- The majority of men who are HIV positive have been infected through the penis
- There is conclusive epidemiological evidence to show that uncircumcised men are at a much greater risk of becoming infected with HIV than circumcised men
- The inner surface of the foreskin contains Langerhans' cells with HIV receptors; these cells are likely to be the primary point of viral entry into the penis of an uncircumcised man
- Male circumcision should be seriously considered as an additional means of preventing HIV in all countries with a high prevalence of infection
- The development of HIV receptor blockers, which could be applied to the penis or vagina before intercourse, might provide a new form of HIV prevention

Methods

To compile the information for this review a Medline search was done using the terms circumcision, HIV, Langerhans' cells, penis, foreskin, and prepuce, and extensive email correspondence with other researchers was also undertaken. Histological observations were carried out on samples of penile tissue obtained from 13 perfusion fixed cadavers of men aged 60-96 years, seven of whom had been circumcised.

The pathogenesis of sexually acquired HIV infection

Between 75% and 85% of cases of HIV infection worldwide have probably occurred during sexual activity.[7] Most cases of primary HIV infection are thought to involve HIV binding initially to the CD4 and CCR5 receptors found on antigen presenting cells—which include macrophages, Langerhans' cells, and dendritic cells—in the genital and rectal mucosa.

The most widely accepted model for the sexual transmission of HIV is based on infection of the genital tract of rhesus macaques with simian immunodeficiency virus.[8 9] After female macaques are inoculated intravaginally with simian immunodeficiency virus, the virus targets the Langerhans' cells located in the vaginal mucosa. Once infected, these cells fuse with adjacent CD4 lymphocytes and migrate to deeper tissues. Within two days of infection, the virus can be detected in the internal iliac lymph nodes and shortly thereafter in systemic lymph nodes. This ultimately leads to a fatal infection.

Similarly, infection in male macaques occurs when simian immunodeficiency virus is inoculated into the penile urethra or onto the foreskin; the same sequence of cellular events involving the infection of Langerhans' cells is then likely to occur.[9] Infected Langerhans' cells have also been detected in the penile mucosa of male rhesus macaques that have chronic simian immunodeficiency virus infection.[9] In humans, histological studies have identified antigen presenting cells in the mucosa of the inner foreskin and urethra.[10] Therefore it seems likely that antigen presenting cells at these mucosal sites are the primary target for HIV in men.

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Circumcision in ancient Egypt shown on a relief from Saqqara (c 2200 BC). Used with the permission of the Wellcome Institute for the History of Medicine, London

In vitro studies have shown that the CD4 receptor is generally necessary, although insufficient on its own, to permit HIV-1 to enter host cells.[11] The entry of HIV-1 into cells requires an additional chemokine receptor, usually CCR5, although CXCR4 is used by cells that become infected during the later stages of the disease.[12] After primary infection occurs, the virus mutates, which allows it to utilise other chemokine receptors, such as CXCR4, and thus spread to a variety of cell types. However, more than 99% of HIV-1 isolates from acutely infected patients are homologous, indicating that one specific variant is likely to be responsible for most cases of primary HIV infection.[13] HIV variants that are transmitted to other individuals almost invariably use CCR5 as a coreceptor and are therefore named R5 viruses, to reflect their specific requirement for a coreceptor.[14]

How HIV enters the penis

About 70% of men infected with HIV have acquired the virus through vaginal sex, and a smaller number have acquired it from insertive anal intercourse.[7] Thus, on a global scale most men who are HIV positive have acquired the virus via the penis. This raises questions of how HIV enters the penis and why men who are uncircumcised are potentially more susceptible to becoming infected with HIV.

The uncircumcised penis consists of the penile shaft, glans, urethral meatus, inner and outer surface of the foreskin, and the frenulum, the thin band connecting the inner foreskin to the ventral aspect of the glans. A keratinised, stratified squamous epithelium covers the penile shaft and outer surface of the foreskin. This provides a protective barrier against HIV infection. In contrast, the inner mucosal surface of the foreskin is not keratinised[15] and is rich in Langerhans' cells,[10] making it particularly susceptible to the virus. This is particularly important because during heterosexual intercourse the foreskin is pulled back down the shaft of the penis, and the whole inner surface of the foreskin is exposed to vaginal secretions, providing a large area where HIV transmission could take place.

There is controversy about whether the epithelium of the glans in uncircumcised men is keratinised; some authors claim that it is not,[15] but we have examined the glans of seven circumcised and six uncircumcised men, and found the epithelia to be equally keratinised. In circumcised males only the distal penile urethra is lined with a mucosal epithelium. However, this is unlikely to be a common site of infection because it contains comparatively few Langerhans' cells.[10]

Ulcerative or inflammatory lesions of the penile urethra, foreskin, frenulum, or glans that are caused by other sexually transmitted infections may provide additional potential routes for HIV transmission. In uncircumcised males, the highly vascular frenulum is particularly susceptible to trauma during intercourse, and lesions produced by other sexually transmitted infections commonly occur there. Thus, male circumcision further reduces the risk of infection by reducing the synergy that normally exists between HIV and other sexually transmitted infections.[5]

Conclusions

Of the estimated 50 million people infected with HIV worldwide, about half are men, most of whom have become infected through their penises. The inner surface of the foreskin, which is rich in HIV receptors, and the frenulum, a common site for trauma and other sexually transmitted infections, must be regarded as the most probable sites for viral entry in primary HIV infection in men. Although condoms must remain the first choice for preventing the sexual transmission of HIV, they are often not used consistently or correctly, they may break during use, and there may be strong cultural and aesthetic objections to using them. Cultural and religious attitudes towards male circumcision are even more deeply held, but in the light of the evidence presented here circumcising males seems highly desirable, especially in countries with a high prevalence of HIV infection. Although neonatal circumcision is easy to perform, and has a low incidence of complications,[16] it would be 15-20 years before a programme of circumcision had any effect on HIV transmission rates. Circumcision at puberty, as practised by many Muslim communities, would be the most immediately effective intervention for reducing HIV transmission since it would be done before young men are likely to become sexually active.

It may also be time to re-think the definition of "safe sex." Since the penis is the probable site of viral entry, neither infected semen nor vaginal secretions should be allowed to come in contact with the penis, particularly in uncircumcised males. Thus, mutual male masturbation during which a penis is exposed to

the potentially infected semen of another male should be regarded as risky sexual behaviour.

New preventive strategies are needed that could be used by men or women before the onset of intercourse. The disadvantage of topical virucides, such as nonoxinol 9, is that they may cause local irritation and thus increase susceptibility to HIV infection. The development of topically active agents that could block HIV binding sites, such as CCR5, and which could be applied to the penis or vagina to create a "chemical condom," might be more effective and acceptable than any mechanical barrier or surgical intervention.

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Modernising the NHS

Patient care: access

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This is the fifth of seven articles

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Delays for access to care plague our healthcare systems. These delays cause patient dissatisfaction, contribute to staff dissatisfaction, and may lead to worsening clinical outcomes. They are also expensive: patients often consume scarce resources while waiting, there is a cost in maintaining any waiting list; the longer the wait the higher the "fail to show" rate, which represents unused capacity; and, finally, there is the risk that patients waiting will arrive with a more costly clinical condition.

Access to care can be improved. Improving access involves looking at system flexibility or capacity. There are three fundamental methods of gaining capacity in a system of care.

Summary points

- Delays plague all healthcare systems, causing discontent, consuming resources, and worsening clinical outcomes
- Most waiting systems rely on distinguishing between urgent and routine cases and so maintain two queues
- Real improvements in access come about when there is only one queue and it is short enough to ensure prompt treatment for urgent cases
- Improving access involves determining the demand and applying resources to match it or reduce it

Gaining capacity

Firstly, many current systems are characterised by schedules that are filled far in advance of the delivery of care or service. Demand arises from the population served. This demand is generally stratified into "urgent" and "routine" queues. Urgent demand is managed by overfilling an already saturated schedule or by sending that demand to another venue for resolution. Routine demand is put to the end of the queue. Overfilling a full schedule or sending demand to another venue or to the end of the queue infuriates patients, overburdens providers of care, and often just postpones the needed care or service.

Secondly, other systems gain capacity by predicting demand for urgent care or service and holding capacity in anticipation of this need. System capacity is set aside for these predicted demands. This method may solve the urgent need but does so at the expense of an